Certain changes have been made in the claims and the specification in order to comply with the requirements on pages 2 and 3 of the office action. Also, a change has been made in the Abstract of the Disclosure.

As discussed at the interview the general pathway of testosterone metabolism involves the flow from the brain of LHRH (leutinizing hormone releasing hormone) to the pituitary gland where it causes LH (leutinizing hormone) release. This step can be blocked by a LRH antagonist and a superagonist.

Currently Goserelin acetate (Zoladek) and Leuprolide acetate (Lupron) are marketed for the foregoing purpose in the treatment of prostatic carcinoma. The LH then causes release of testosterone from the testicle. For testosterone to have an effect it must first enter a cell and be converted to dihydrotestosterone (DHT). This step can be blocked by finasteride (Proscar). The DHT then binds a carrier and enters the nucleus to influence cell metabolism. This step is blocked by Bicalutamide, Flutamide and Nilutamide.

It has been discovered in the present invention that testosterone metabolism is involved in the development of atherosclerosis. The present invention involves the use of certain drugs to block testosterone's effects so as to decrease atherosclerotic disease. The present invention involves the discovery that there is a decrease in cardiac events (a result of atherosclerosis) in patients who used Goserelin, Finasteride, and Leuprolide for other purposes. It was noted that all these drugs block testosterone metabolism. Thus, the present invention involves the conclusion that any drug that blocked this pathway will have a similar effect.

There was also a discussion at the interview that there is further evidence linking testosterone metabolism and atherosclerosis. It is already known that male pattern baldness is a risk factor for myocardial infarction. The development of male pattern baldness is testosterone dependent and can be prevented by administration of Finasteride (which blocks formation of DHT from testosterone). Further new data which link benign prostatic hyperplasia (BPH), another testosterone dependent disease, to atherosclerosis were presented. Prostatic specific antigen (PSA) is lower in men with less BPH. The data presented showed that there were fewer instances of myocardial infarction and coronary artery angioplasty and bypass in men with lower PSA's.

The following is the additional data:

Additional Data:

The charts of 702 male patients were reviewed. 140 patients met the stated inclusion-exclusion criteria. 32 patients had PSA levels $\leq$1.0 ug/L and 108 subjects had PSA>1.0 ug/L but less than 10.0 ug/L. Table 1 summarizes the frequency of some of the measured variables between the 2 groups.

There were no significant differences in the incidence of accepted risk factors for atherosclerosis between the two groups, including age, hypertension, diabetes mellitus, smoking, and parental history of MI. (Table 1). Patients with PSA $\leq$1.0 ug/L had significantly lower incidence of self reported MI and CABG compared to those with PSA levels between 1.1 and 10.0 ug/L (9% vs. 29% $p<0.03$).

Table 1: Subjects' Data

Variables	PSA≤1.0	PSA 1.1-10.0	Statistically
Mean Age (yrs.)	71.6±5.1	72.2±4.2	significant
	#positive/N	#positive/N	
Smoking History	24/31 (77%)	82/107(77%)	NO
Diabetes Mellitus	8/27 (30%)	13/87 (15%)	NO
Antihypertensive medications	12/30 (40%)	47/106 (44%)	NO
Parental history of MI	6/30 (20%)	30/106 (28%)	NO
History of Stroke or TIA	4/32 (13%)	11/106 (10%)	NO
History of CAD (coronary artery disease)	3/32 (9%)	31/108 (29%)	YES

± - standard division N - the number of subjects for which data is available

The last entry in Table 1 shows a decrease from 29% to 9% in the history of CAD and such decrease is attributable to the administration of drugs which block testosterone metabolism.

Methods:

Charts from male patients seen in a urology practice over a 2-year period (1996-1998) were reviewed. Data was extracted from patient charts and laboratory reports including age, smoking habit, presence of diabetes, and medication history. In addition, history of coronary angioplasty, myocardial infarction (MI), stroke, transient ischemic attack

(TIA), parental history for MI, transurethral resection of the prostate (TURP), prostate biopsy, and serum PSA values were obtained.

Patients were eliminated from the study if they were younger than 65 years old or older than 80. In order to ensure that serum PSA reflected the volume of BPH, patients were excluded from analysis if they had used finasteride since this drug can independently reduce PSA levels. Patients were also excluded if they were within 6 months of any condition or procedure known to influence serum PSA. No patient who had undergone TURP was included. Patients with PSA's of 40.0-10.0 ug/L were included only if at least one prostate biopsy had been negative. No patient with prostatic carcinoma was included. Patients with PSA values of >10 ug/L were felt to be at risk for prostatic carcinoma despite negative biopsies and were not included. Patients who had taken medication to lower serum lipids were eliminated since these medications can independently alter cardiac risks (17, 18).

Serum PSA was measured using Microparticle Enzyme Immunoassay (MELA, Abbot Laboratories). Patients were categorized into two groups based on their PSA levels. Group one consisted of those patients with a PSA of 1.0 ug/L or less (no BPH present) and group two consisted of patients with a PSA greater than 1.0 ug/L but less than 10.0 ug/L (BPH present).

Patients were considered to have coronary artery disease (CAD) if they gave a history of either ML, coronary artery bypass grafting (CABG), or coronary angioplasty.

Data analysis:

Data was analyzed using Chi Square statistics, and unpaired student t-test. $P<0.05$ was considered significant. Data is presented as mean ± standard deviation.

CONCLUSION:

It is believed that the Examiners at the interview were satisfied that the foregoing data demonstrates the patentability of the claims. Accordingly, the issuance of a Notice of Allowance is respectfully requested.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

November 9, 1999

By _____
Alan H. Bernstein
Reg. No. 19,315
12th Floor, Seven Penn Center
1635 Market Street
Philadelphia, PA 19103-2212
Attorneys for Applicant

CERTIFICATE OF MAILING

I hereby certify that the foregoing AMENDMENT, re application Serial No. 09/089,583 is being deposited with the United States Patent and Trademark Office as First Class Mail, postage prepaid, in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, this 9th day of November, 1999.

_____
Alan H. Bernstein

4/

References:

1. Castelli WP. Cardiovascular disease in women. Am J Obstet Gynecol 1988;158:1553-60
2. Grodstein F, Stampfer MJ, Colditz GA, Willett WC, Manson JE, Joffe M, et al. Postmenopausal hormone therapy and mortality. New Engl J Med 1997;336:1769-75
3. Guzick DS, Talbott EO, Sutton-Tyrrell K, Herzog HC, Kuller LH, Wolfson SK Jr. Carotid atherosclerosis in women with polycystic ovary syndrome: Initial results from a case-control study. Am J Obstet Gynecol 1996;174:1224-32
4. Ford ES, Freedman DS, Byers T. Baldness and ischemic heart disease in a national sample of men. Am J Epidemiol 1996;143:651-7
5. Lesko SM, Rosenberg L, Shapiro S. A case-control study of baldness in relation to myocardial infarction in men. JAMA 1993;269:998-1003
6. Brodland DG, Muller SA. Androgenic alopecia Cutis 1991;47(3):173-6
7. Berry M. Epidemiology of Prostatic Hyperplasia. 1997, AUA Update Series Vol XVI Lesson 35
8. Gormley GJ. Finasteride: a clinical review. Biomed Pharmacol 1995;49:319-24
9. McConell JD etal, The effect of Finasteride on the risk of acute urinary retention NEJM 1998;338:557
10. Bosch RJ, Griffiths DJ, Blom JM, Schroeder FH. Treatment of benign prostatic hyperplasia by androgen deprivation: effects on prostate size and urodynamic parameters. J Urol 1989;141:68-7
11. McNeal JE. Pathology of benign prostatic hyperplasia: insight into etiology, Urol Clin N Amer 1990;17:477-486

12. Rimm EB, Stumpfer MJ, Giovannucci E, Ascherio A, Spiegelman D, Colditz GA, Willet WC. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. Am J Epidemiol 1995;141:1117-27

13. Giovannucci E, Rimm EB, Chute CG, Kawachi I, Colditz GA, Stampfer MJ, Willett WC. Obesity and benign prostatic hyperplasia. Am J Epidemiol 1994;140:989-1002.

14. Rohr HP, Bartach G Human benign prostatic hyperplasia: a stromal disease: New perspectives by quantitaive morphology. Urology 1980;16(6):625-633.

15. Gould L, Claus G, Relationship between prostatic volume and serum prostatic specific antigen in men with clinical BPH. J Urol 1998;159:5 pg 109

16. Hochberg DA, Bassillotte JB, Erachia JA. Prostate specific antigen as a surrogate for prostate volume in patients with biopsy proven benign prostatic hyperplasia. J Urol 1999;161:4 pg287

17. Downs JR, Clearfiled M, Weiss S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. results of AFCAPS/TexCAPS. JAMA 1998;279:1615-22

18. Scandinavian Simvastatin Survival Study Group. The Lancet 1994;344:1383-9

19. Mendelsohn ME, Karas RH The protective effects of estrogen on the cardiovascular system. JAMA 1999;340:1801-1811

20. Bagatell CJ, Bremner WJ. Androgen and progestagen effects on plasma lipids. Progress in Cardiovascular Diseases. 1995; 38 (3):255-71

21. Haffner SM, Valdez RA. Endogenous sex hormones: impact on lipids, lipoproteins, and insulin. American Journal of Medicine. 1995:98(1A):40S-47S

22. Campbell JH, Campbell GR. The cell biology of atherosclerosis- New Developments Australian and New Zealand J Med 1997;27:497-500

22. Rubins HP, Robins ST, CollinsD, et al. Distribution of lipids in 8,500 men with coronary artery disease. Am J Cardiol 1995;75:1196-201

23. Samjen D, Kohen F, Jaffe A, Amir-Zaltzman Y, Knoll E, Stern N. Effects of gonadol steroids and their antagonists on DNA synthesis in human vascular cells. Hypertension 1998;32:39-45

24. Fujimoto R, Morimoto I, Morita I, Sugimoto H, Ito Y, Eto S. Androgen receptors, 5 alpha-reductase activity and androgen-dependent proliferation of vascular smooth muscle cells. J Steroid Biochemistry and Molecular Biology 1994;50:169-74

Last page